Enantioselective Norrish – Yang Cyclization Reactions of *N*-(*ω*-Oxo-*ω*-phenylalkyl)-Substituted Imidazolidinones in Solution and in the Solid State

Thorsten Bach,*[a] Tobias Aechtner,[a] and Bernhard Neumüller[b]

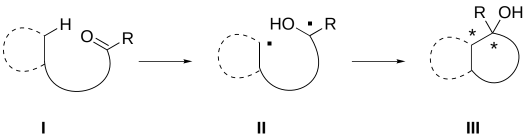
In memory of J. Jens Wolff

Abstract: The four *N*-(*ω*-oxo-*ω*-phenylalkyl)-substituted imidazolidinones **5** – **8** were prepared from *N*-acetylimidazolidinone (**4**). Upon irradiation, these substrates underwent Norrish – Yang cyclization to the racemic products *rac*-**9** – *rac*-**12** (51 – 75 %). The reactions of the *N*-2-oxoethylimidazolidinones **5** and **6** were conducted in *t*BuOH, and yielded 1:1 mixtures of *exo*/*endo* diastereoisomers *rac*-**9a**/*rac*-**9b** and *rac*-**10a**/*rac*-**10b**, accompanied by Norrish type II cleavage products. The reactions of the *N*-3-oxopropylimidazolidinones **7** and **8** were performed in toluene. The *exo* diastereoisomers *rac*-**11a** and *rac*-**12a** were the major diastereoisomers (d.r. ≅4:1). In the presence of the chiral compounds **1** – **3**, the photocyclization of substrate **8** proceeded with significant enantiomeric excess (5 – 60 % *ee*). The more sophisticated complexing agents **3** and *ent*-**3** provided better enantiofacial differentiation (up to 60 % *ee*) than the lactams **1** and **2** (up to 26 % *ee*). Low temperatures and an excess of the complexing agent helped to increase the enantioselectivity. The absolute configuration of the major *exo* product **12a** obtained from compound **8** in the presence of complexing agent **3** was unambiguously established by single-crystal X-ray crystallography of its chiral *N*-methoxyphenylacetyl derivative **15a**. In a similar fashion, the absolute configurations of the *endo* products **12b** and *ent*-**12b** were established. The *N*-2-oxoethylimidazolidinone **5**, which crystallized in a chiral space group, was irradiated in the solid state. At low levels of conversion, the product **9a**/*ent*-**9a** was formed with high enantiomeric excess (78 % *ee*). The enantioselectivity deteriorated at higher levels of conversion.

Keywords: asymmetric synthesis · cyclization · hydrogen bonds · photochemistry · radical reactions

Introduction

Photoexcited carbonyl compounds can abstract hydrogen atoms either inter- or intramolecularly. The subsequent reactions initiated by this primary step have been intensively studied in mechanistic photochemistry and are fairly well understood.[1] In 1958, Yang and Yang reported on an intriguing intramolecular carbon – carbon bond-forming reaction resulting from intramolecular hydrogen abstraction by a photoexcited ketone.[2] The reaction was shown to be a general process[3] and is depicted in Scheme 1 by the transformation **I** → **III**. Different names for the reaction have been coined over the years, including Yang photocyclization, Type II cyclization, and Norrish – Yang cyclization. Mechanistically, a 1,*n*-biradical **II**—the two radical centers of which are in many cases prostereogenic—is involved as an intermediate. As a consequence, two stereogenic centers are formed in the course of the reaction. These are marked by asterisks (*) in formula **III**.



Scheme 1. Intramolecular hydrogen abstraction in a photoexcited ketone **I** to give the intermediate biradical **II** and subsequent cyclization to product **III**.

From a product-oriented point of view, the site of hydrogen abstraction determines the size of the resulting ring. The facile γ-hydrogen abstraction, proceeding through a six-membered transition state, affords four-membered rings (cyclobutanes, oxetanes, azetidines, etc.). This process is frequently accompanied by the Norrish type II cleavage reaction.[1] If there is no hydrogen atom available in the γ position to the carbonyl group, δ- or ε-hydrogen atom abstractions occur. The subsequent cyclization results in five- or six-membered rings.

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A further division can be made on the basis of the location of the carbonyl group and the hydrogen atom. It has been shown that the restricted free rotation in endocyclic bonds significantly influences the kinetics of hydrogen atom abstraction.[4]

The synthetic utility of the Norrish–Yang cyclization has been beautifully demonstrated in several examples.[5] In recent years, the stereoselectivity of the reaction has attracted considerable attention and has been closely studied. The simple diastereoselectivity associated with the relative configurations of the two newly formed stereogenic centers can be interpreted in steric terms.[3, 6] The more bulky substituents at the newly formed ring are in a *trans* relationship. Because of hydrogen bonding, the effective size of the hydroxyl group is dependent on the solvent, the group acting as a large substituent in protic solvents such as *t*BuOH and as a small substituent in aprotic, nonpolar solvents such as toluene (see below).[6e, 7] The facial diastereoselectivity can be controlled by stereogenic centers in the chain. Conformation restriction in cyclic systems and 1,3-allylic strain have proven to be efficient control elements.[3, 8] Intramolecular hydrogen bonds have been invoked to account for the stereo- and chemoselectivity of Norrish–Yang cyclizations.[8a,c] Stereoselective Norrish–Yang cyclizations of α-ketoesters have been performed with retention of configuration at a stereogenic center ("chiral memory effect").[9]

Abstract in German: *Die vier N-(ω-oxo-ω-phenylalkyl)substituierten Imidazolidinone **5**–**8** wurden ausgehend von N-Acetylimidazolidinon (**4**) hergestellt und reagierten bei Bestrahlung unter Norrish–Yang-Cyclisierung zu den racemischen Produkten rac-**9**–rac-**12** (51–75%). Die Reaktion der N-2-Oxoethylimidazolidinone **5** und **6** wurde in tBuOH durchgeführt und ergab ein 1:1-Gemisch der exo/endo-Diastereoisomere rac-**9a**/rac-**9b** und rac-**10a**/rac-**10b** sowie Produkte der Norrish Typ II-Spaltung. Die Reaktion der N-3-Oxopropylimidazolidinone **7** und **8** konnte in Toluol als Lösungsmittel durchgeführt werden. Die exo Diastereoisomere rac-**11a** und rac-**12a** waren die Hauptdiastereoisomere (d.r. ≅ 4:1). In Gegenwart der chiralen Verbindungen **1**–**3** verlief die Photocyclisierung des Substrats **8** mit deutlichem Enantiomerenüberschuß (5–60% ee). Die neu entwickelten Komplexierungsreagentien **3** und ent-**3** lieferten eine bessere Differenzierung der enantiotopen Seiten (bis zu 60% ee) als die Lactame **1** und **2** (bis zu 26% ee). Eine niedrige Reaktionstemperatur sowie ein Überschuß der Wirtverbindung begünstigen eine hohe Enantioselektiviät. Die Absolutkonfiguration des Hauptprodukts **12a**, das durch Umsetzung von Verbindung **8** in Gegenwart des Wirtes **3** erhalten wurde, wurde durch Kristallstrukturanalyse seines chiralen N-Methoxyphenylacetylderivats **15a** einwandfrei belegt. In ähnlicher Weise wurde die Absolutkonfiguration der endo Produkte **12b** und ent-**12b** bestätigt. Das N-2-Oxoethylimidazolidinon **5**, das in einer chiralen Raumgruppe kristallisiert, wurde als Feststoff bestrahlt. Bei niedrigem Umsatz wurde das Produkt **9a**/ent-**9a** mit hohem Enantiomerenüberschuß (78% ee) gebildet. Die Enantioselektivität verschlechterte sich bei steigendem Umsatz.*

Enantioselective variants of the photocyclization have been successfully conducted in the solid state.[10] If the precursor for the cyclization crystallizes in a chiral space group, it is possible to isolate homochiral crystals, irradiation of which can give rise to enantiomerically enriched products.[11, 12] Alternatively, crystallization in a chiral space group can be induced by a chiral counterion (ionic chiral auxiliary).[13] This approach reliably delivers enantiomorphically pure crystals and guarantees high enantioselectivities,[14] but it requires the presence of an acidic or basic functional group in the reactant. Finally, Norrish–Yang cyclizations have also been performed in the cavities of optically active host molecules.[15] Host–guest inclusion crystals can be prepared simply by mixing the host crystals[16, 17] with the corresponding substrate. Zeolites into which a chiral inductor and the substrate have been deposited have been employed in a similar fashion.[18] Enantiotopic or enantiofacial differentiation in all solid-state reactions depends on restricted motion of the chain connecting the reacting centers. The observed enantioselectivity is due to a homochiral helical structure of the side chain, into which the molecule is forced by the chiral environment.

In solution photochemistry, the situation is different. Biradicals such as **II** (Scheme 1) are expected to rotate freely, and facial differentiation is to be provided by the chiral environment of a complexing agent. To the best of our knowledge, no significant enantioselectivities (>10% *ee*) have yet been recorded for the Norrish–Yang cyclization in solution.[17] Enantiomerically pure or enantiomerically enriched products have, however, been obtained from prochiral substrates by attachment of a covalently bound auxiliary, a subsequent photocyclization, and final removal of the auxiliary.[19]

In this paper, we report on the first example of an enantioselective Norrish–Yang cyclization in solution. The method is based on the use of chiral complexing agents **1**–**3** (Figure 1) capable of binding a prochiral substrate through hydrogen bonds.

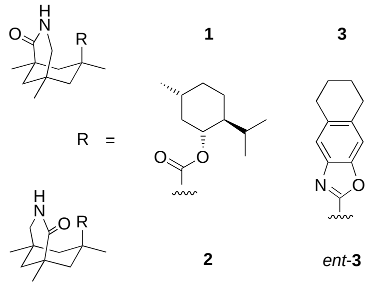
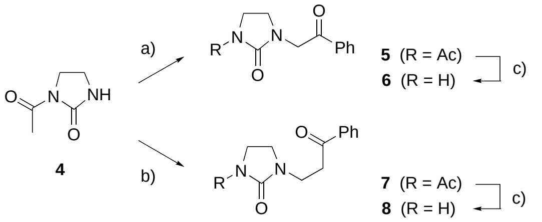


Figure 1. The structures of host compounds **1**–**3**, which are capable to differentiate enantiotopic faces in photochemical reactions of hydrogen-bound substrates.

Preliminary results had revealed that hosts **1** and **2** can induce detectable enantioselectivities (up to 26% *ee*) in Norrish–Yang cyclizations.[20] The more sophisticated hosts **3** and *ent*-**3** have recently been developed[21] and proved to be superior to compounds **1** and **2** in enantioselective photochemical cycloaddition reactions.[22] Their applicability to a Norrish–Yang cyclization has now been tested and the enantioselectivity (up to 60 % *ee*) and the simple diastereoselectivity of the reaction studied. The relative and the absolute configurations of the products were unequivocally established. These data support a mechanistic picture of the enantiofacial differentiation, based on coordination of the photoactive substrate to the host. In addition, we incidently found that a potential Norrish – Yang cyclization substrate crystallized in a chiral space group. An enantioselective solid-state photocyclization (up to 78 % *ee*) was performed with this compound. The results of this study are also reported.

Results and Discussion

Selection of suitable substrates: The chiral hosts depicted in Figure 1 require a substrate with a lactam or amide unit for effective hydrogen bonding. We considered the unsymmetrically substituted imidazolidinones **6** and **8**, depicted in Scheme 2, to be well suited for this purpose. They have appropriate binding sites and should undergo efficient γ- (**6**) or δ-hydrogen (**8**) abstraction reactions. Indeed, related five-membered lactams have previously been shown to yield Norrish – Yang cyclization products upon irradiation.[7b,c] The synthesis of the desired products commenced with the readily available monoacetylated imidazolidinone **4**.[23] N-Alkylation with phenacyl bromide[24] delivered the *N*-acetyl protected ketone **5**, which was hydrolyzed to yield the unprotected imidazolidinone **6**. In an analogous fashion, the starting material **4** was converted into ketone **7** by conjugate addition to phenyl vinyl ketone.[25] This intermediate was saponified to yield *N*-(3-oxo-3-phenylpropyl)imidazolidin-2-one (**8**). Although the yields for the N-functionalization of compound **4** remained low in both cases, the brevity of the chosen synthesis is an advantage. Multigram quantities of the desired substrates were readily available by this route. Alternative syntheses were consequently not pursued.



Scheme 2. Preparation of the Norrish – Yang cyclization substrates **6** and **8**: a) NaH (1.1 equiv), $BrCH_2COPh$ (1.5 equiv), KI (cat.) in THF, 70 °C, 20 h, 40 %; b) $PhCOCH_2CH_2NMe_2 \cdot HCl$ (0.5 equiv), *p*TsOH (cat.) in *o*-xylene, reflux, 6 h, 33 %; c) NaOH (excess) in $MeOH/H_2O$, 50 °C, 2 h. **6**: 83 %; **8**: 79 %.

Single-crystal structure analysis revealed that compound **5** crystallizes in a chiral space group ($P2_12_12_1$).[26] As Figure 2 shows, the carbonyl group of the phenyl ketone moiety points towards one of the two enantiotopic hydrogen atoms at the prostereogenic carbon atom. The orientation is due to a rotation of the exocylic 2-phenyl-2-oxoethyl group around the C–N bond, which is restricted in the crystal. The resulting dihedral angle is 82°. On the basis of this finding, we investigated the solid-state photochemistry of compound **5** (see below).

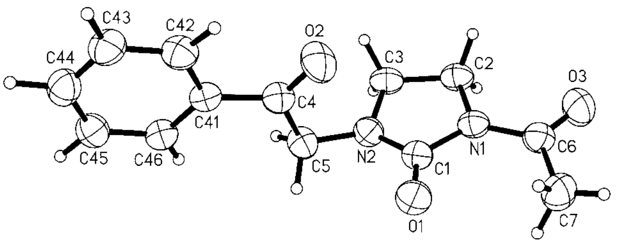
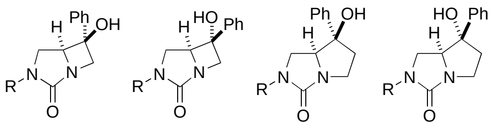


Figure 2. A molecule of compound **5** in the crystal.

The photocyclization of the ketones **5**, **6**, **7**, and **8** was initially studied in an achiral environment to assess the products and to separate the racemic diastereoisomers. To this end, solutions of the substrates in toluene, acetonitrile, or *t*BuOH were irradiated at room temperature (quartz tubes, light source: Rayonet RPR-3000 Å). The solubility of the 2-oxoethyl substrates **5** and **6** in toluene is extremely low. The irradiation experiments were consequently conducted in *t*BuOH as the solvent. The products were obtained as mixtures of racemic diastereoisomers *rac*-**9** and *rac*-**10** (Figure 3), which could be separated by flash chromatography. Their relative configurations were assigned by NMR experiments and by single-crystal X-ray analysis (see below). The Norrish – Yang cyclization was in both cases accompanied by Norrish type II cleavage reactions. Acetophenone and the corresponding unsaturated imidazol-2-ones were isolated as side products. The imidazolones could easily be separated and quantified (25 % yield). If the data for **6** and **8** (entries 2 and 6 in Table 1) are compared, the difference in yield can be attributed to the formation of cleavage products in the case of the former substrate. In acetonitrile as the solvent the reaction of compound **6** proceeded sluggishly.



rac-**9a** *rac*-**9b** (R = Ac) *rac*-**11a** *rac*-**11b**
rac-**10a** *rac*-**10b** (R = H) *rac*-**12a** *rac*-**12b**

Figure 3. Photocyclization products **9** – **12** obtained from irradiation of the *N*-(ω-oxo-ω-phenylalkyl)imidazolinones **5** – **8** (cf. Table 1).

Table 1. Simple diastereoselectivity in the Norrish – Yang cyclization of various *N*-(ω-oxo-ω-phenylalkyl)substituted imidazolidinones (see Figure 3.

	Ketone[a]	Solvent	*c* [M]	Yield[b] [%]	Product	*exo*:*endo*
1	**5**	*t*BuOH	2.5×10^{-2}	66	*rac*-**9**	47:53
2	**6**	*t*BuOH	2.5×10^{-2}	51	*rac*-**10**	53:47
3	**7**	toluene	5×10^{-3}	55	*rac*-**11**	73:27
4	**8**	toluene	5×10^{-3}	73	*rac*-**12**	88:12
5	**8**	MeCN	2.5×10^{-2}	61	*rac*-**12**	62:38
6	**8**	*t*BuOH	2.5×10^{-2}	75	*rac*-**12**	39:61

[a] The reactions were carried out by irradiation for 3 h in a merry-go-round apparatus (irradiation source: Rayonet RPR-3000 Å). [b] Yield of isolated product.

A further advantage of substrate **8** as compared to substrate **6** is its superior solubility in apolar solvents such as toluene. As irradiation experiments in the presence of chiral hosts are best conducted in apolar solvents, imidazolidinone **8** was selected as the substrate for the enantioselective photocyclization reactions. The simple diastereoselectivity of its photocyclization to product *rac*-**12** changed upon changing the solvent (entries 4, 5, and 6). In toluene, the thermodynamically more stable *exo* compound *rac*-**12a**, in which the phenyl group and the imidazolidinone ring are *trans*-oriented, is clearly the major product (d.r. 88:12). In *t*BuOH, the diastereoselectivity is in favor of the *endo* product *rac*-**12b**, although the preference is less pronounced. In acetonitrile there is a small preference for the *exo* product (entry 5). As already mentioned in the Introduction, one explanation for the solvent-dependence of the selectivity is based on the relative size of the phenyl group and the hydroxy group.[6, 7] The size of the hydroxy group is increased by hydrogen bonding in *t*BuOH, and slightly overrides the steric bulk of the otherwise larger phenyl group. The conversion of the *N*-acetyl derivative **7** of compound **8** was conducted in toluene as the solvent (entry 3). The yield and the simple diastereoselectivity are comparable to the results recorded for the deacetylated compound. The *exo* compound *rac*-**11a** was required for the structural elucidation of the *exo* compound **12a** (see below).

The assignment of relative configurations for the products **9**–**12** was based on ^{1}H NMR NOESY measurements, details of which are provided in the Experimental Section. In addition, crystal structures of two products became available in the course of our investigation. Figure 4 depicts the structure of product *rac*-**10b**, which was the major diastereoisomer obtained from photocyclization of ketone **6** in *t*BuOH. The structure nicely shows the *endo* relationship of the phenyl group to the imidazolidinone ring.[27]

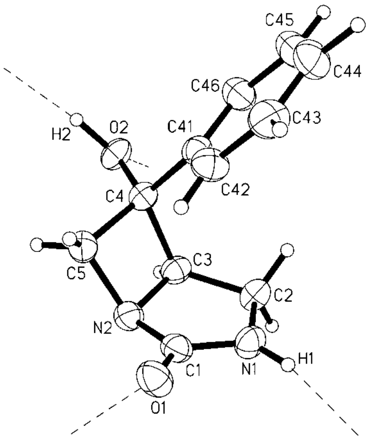


Figure 4. A molecule of *endo* product *rac*-**10b** in the crystal.

Figure 5 provides a picture of the relative configuration of compound *rac*-**12a**. This product was isolated as the major diastereoisomer from the photocyclization of ketone **8** in toluene as solvent. The phenyl group is located *exo* relative to the imidazolidinone ring.[28]

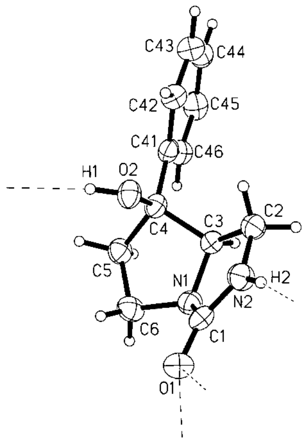
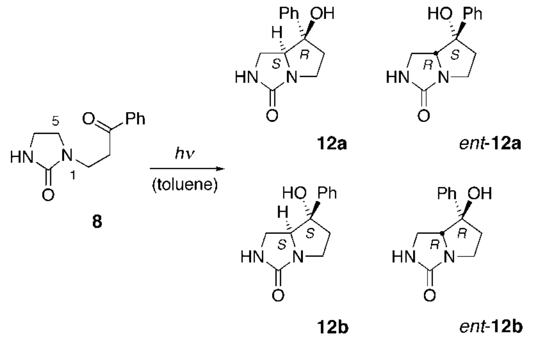


Figure 5. A molecule of *exo* product *rac*-**12a** in the crystal.

Enantioselective Norrish–Yang cyclization of imidazolidinone 8 in solution: From the preliminary experiments described in the previous section it became clear that imidazolidinone **8** was superior to its analogue **6** with regard to potential use in enantioselective photocyclization reactions. The product yields were higher and, more importantly, the substrate was more soluble in toluene. All experiments in the presence of chiral hosts **1**–**3** were consequently conducted with the former substrate. For clarity, Scheme 3 depicts the products to be expected from the Norrish–Yang cyclization of **8**.



Scheme 3. Enantioselective Norrish–Yang cyclization reaction of substrate **8** to the possible products **12a**, *ent*-**12a**, **12b**, and *ent*-**12b** (cf. Table 2).

The data recorded for the enantioselective photocyclization in the presence of compounds **1**–**3** are summarized in Table 2. The simple diastereoselectivity was determined from the crude product by integration of appropriate ^{1}H NMR signals. In all cases, the major products were the *exo* diastereoisomers **12a** or *ent*-**12a**, the *exo*:*endo* ratios varying around 4:1. There was no significant temperature influence on the simple diastereoselectivity, as is evident from entries 1–3. The enantioselectivity was determined after separation of the diastereoisomers. The enantiomeric excess (*ee*) of the major *exo* diastereoisomer was determined by HPLC on a chiral stationary column (Nucleodex β-OH). The *ee* increased at lower temperature, the best value obtained with host **1** being 26% *ee* in favor of enantiomer **12a** (entry 3). The diastereoisomer **2** of host **1** behaved as if it was its enantiomer and delivered the enantiomeric major product *ent*-**12a** in almost

Table 2. Enantioselectivity in the Norrish–Yang cyclization of imidazolidinone **8** in the presence of chiral hosts **1**–**3** (cf. Scheme 3).

	Host[a]	Equiv	T [°C]	Product[b]	Yield[c] [%]	ee[d] [%]	*exo*:*endo*
1	**1**	2.5	30	**12a**	86	5	88:12
2	**1**	2.5	−10	**12a**	77	16	77:23
3	**1**	2.5	−45	**12a**	77	26	79:21
4	**2**	2.5	−45	*ent*-**12a**	77	25	84:16
5	**3**	1.0	−45	**12a**	72	37	85:15
6	**3**	2.5	−45	**12a**	70	60	80:20
7	*ent*-**3**	2.5	−45	*ent*-**12a**	72	59	82:18

[a] The reactions were carried out by irradiation for 12–20 h with toluene as the solvent (quartz glass; liquid-cooled irradiation source: Original Hanau TQ-150). [b] Major stereoisomer. [c] Yield of isolated product. [d] The enantiomeric excess of the major *exo* diastereoisomer was determined by HPLC (see Experimental Section).

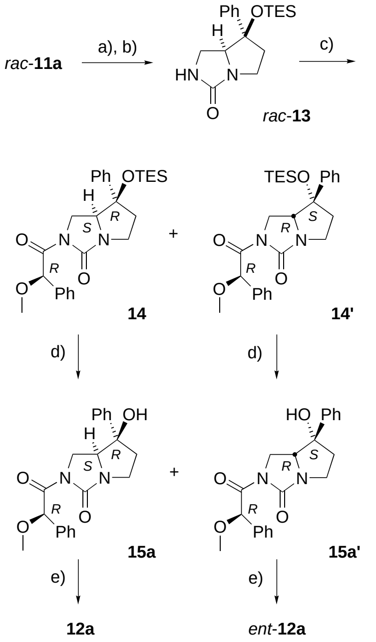
identical optical purity (entry 4). Compounds **3** and *ent*-**3** were superior to compounds **1** and **2** with regard to enantiofacial differentiation. Under otherwise identical conditions, compound **3** induced an enantiomeric excess of 60% *ee* (entry 6). The major enantiomer we obtained was compound **12a**. Within the error limit, its enantiomer *ent*-**3** delivered the same *ee* (entry 7), predominantly yielding the product *ent*-**12a**. Because of decreased host–substrate association, the *ee* dropped significantly upon reducing the molar ratio of host to substrate (entry 5).

The absolute configurations of the products were determined by X-ray crystallography. To this end, derivatives of the products bearing substituents of known absolute configuration were prepared. Selective N- or O-functionalization of the *exo* compound *rac*-**12a** was difficult. The O-silylated compound *rac*-**13** was therefore prepared from the N-acetyl compound *rac*-**11a**, which was in turn available by photocyclization of **7** (see above). Triethylsilyl triflate (TESOTf) was the silylating agent of choice with which to attach a base-stable silyl group to the sterically congested tertiary alcohol (Scheme 4).

Subsequent hydrolysis under basic conditions delivered the silyl ether *rac*-**13**, which was subsequently N-acylated with (*R*)-*O*-methylmandelic chloride,[29] with lithium hexamethyldisilazide (LHMDS) as the base.[30] The two diastereoisomers **14** and **14′** were separated by flash chromatography. They were independently converted into the free alcohols **15a** and **15a′** by silyl deprotection with tetrabutylammonium fluoride (TBAF). Crystals of compound **15a** were suitable for single-crystal X-ray crystallography; the structure of this compound is depicted in Figure 6. It proves the absolute configuration of the two stereogenic centers within the diazabicyclo[3.3.0]octane (pyrrolo[1,2-*c*]imidazole) ring.[31]

The separate diastereoisomers **15a** and **15a′** were saponified to yield the enantiomerically pure products **12a** and *ent*-**12a**. Their correlation with the photocycloaddition products (Scheme 3) through the HPLC data was facile. The major enantiomer obtained from the Norrish–Yang cyclization in the presence of hosts **1** or **3** is consequently (5*S*,6*R*)-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (**12a**).

The *endo* diastereoisomers **12b** and *ent*-**12b** were isolated in minor quantities from the photocyclization experiments. Their *ee* value was not determined in every run. In the cases in which it was done, the *ee* was significantly lower than the *ee* of the *exo* diastereoisomer. In addition, if **12a** was the major *exo* enantiomer, product **12b** was always the major *endo* enantiomer. Analogously, product *ent*-**12a** was accompanied predominantly by *ent*-**12b** and not by **12b**. As an example, *endo* product **12b** was obtained upon photocyclization of compound **8** in the presence of 2.5 equivalents of host **3** at −45 °C (entry 6 in Table 2). Its *ee* was 30% as compared to 60% *ee* for the *exo* compound **12a**.



Scheme 4. Structural elucidation of the *exo* cyclization products **12a** and *ent*-**12a**. a) TESOTf (3.0 equiv), 2,6-lutidine (3.2 equiv) in CH_2Cl_2, 0 °C → RT, 14 h, b) K_2CO_3 (1.5 equiv) in MeOH, RT, 3 h, 55% (two steps); c) LHMDS (1.2 equiv), (*R*)-*O*-methylmandelic chloride (2.4 equiv) in THF, −78 °C → RT, 2 h (**14**: 39%, **14′**: 39%); d) TBAF (1.1 equiv) in THF, RT, 1.5 h (**15a**: 89%, **15a′**: 86%); e) K_2CO_3 (1.5 equiv) in MeOH, RT, 2.5 h (**12a**: 84%, *ent*-**12a**: 85%).

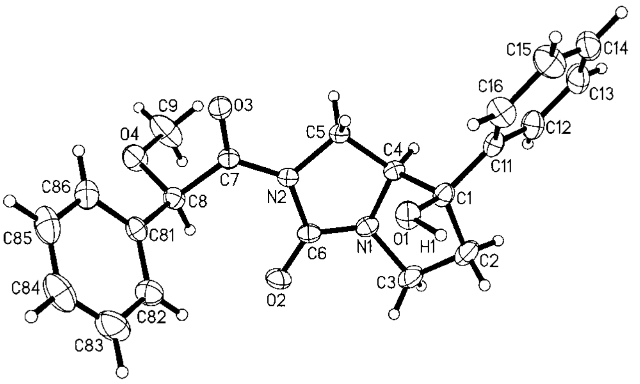
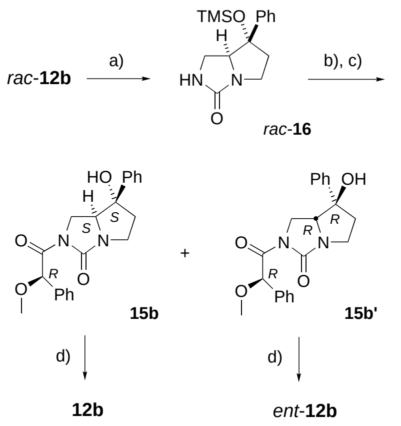


Figure 6. A molecule of compound **15a** in the crystal.

The assignment of the absolute configuration for the *endo* diastereoisomers was again based on crystallographic evidence. O-Silylation of compound *rac*-**12b** with trimethylsilyl chloride (TMSCl) was facile, and produced the silyl ether *rac*-**16** (Scheme 5). In analogy to compound *rac*-**13**, the imidazolidinone was acylated with the chiral (*R*)-*O*-methylmandelic chloride and O-deprotected. The separation of the two diastereoisomers **15b** and **15b′** by flash chromatography was



Scheme 5. Structural elucidation of the *endo* cyclization products **12b** and *ent*-**12b**. a) TMSCl (1.3 equiv), imidazole (1.5 equiv) in DMF, 0 °C, 3.5 h, 73 %; b) LHMDS (1.2 equiv), (*R*)-*O*-methylmandelic chloride (2.4 equiv) in THF, – 78 °C → RT, 2 h; c) TBAF (1.1 equiv) in THF, RT, 2 h, 79 % (two steps, **15b**/**15b′** 1:2). (d) K_2CO_3 (1.5 equiv) in MeOH, RT, 2.5 h (**12b**: 78 %, *ent*-**12b**: 84 %).

not total, but fractions containing diastereomerically pure material were obtained. The pure diastereoisomer **15b′** delivered crystals suitable for X-ray crystallography.[20] Saponification of compound **15b′** yielded the (5*R*,6*R*)-enantiomer *ent*-**12b**.

CD spectra of the enantiomerically pure diazabicyclo-[3.3.0]octanes **12a**, *ent*-**12a**, **12b**, and *ent*-**12b** were recorded (Figure 7). Compound **12a**, with the (5*S*,6*R*) configuration, showed a Cotton effect around 217 nm. The negative circular dichroism $\Delta\varepsilon$ (217 nm) was determined as -9.8. A small

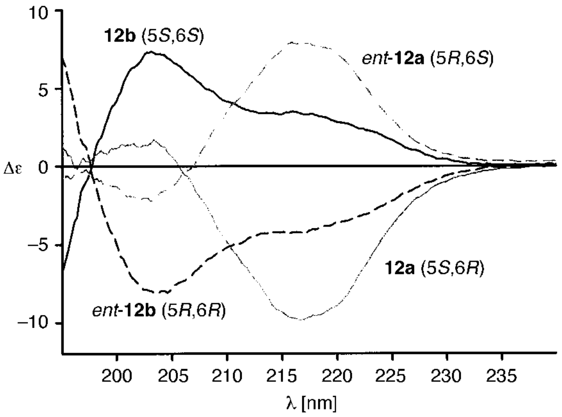


Figure 7. CD spectra of compounds **12a**, *ent*-**12a**, **12b**, and *ent*-**12b**.

positive CD was observed at 203 nm ($\Delta\varepsilon = 1.4$). The diastereoisomeric compound **12b**, with the (5*S*,6*S*) configuration, exhibited an extensive Cotton effect with a positive CD ($\Delta\varepsilon$ (203 nm) = 7.4) between 200 and 230 nm and a shoulder at 216 nm ($\Delta\varepsilon = 3.3$). From comparison of the two diastereoisomers, it appears that the direction of the CD depends on the absolute configuration at the stereogenic center in the 6-position, located adjacent to the phenyl chromophore.

Differentiation of the enantiotopic faces: The structural data described above support the idea of enantiofacial differentiation by the host compounds through hydrogen bonds. If, as has previously been shown for related cases,[32] the host (e.g. **3**) binds the substrate **8** in a 1:1 fashion, the intermediate biradical **17** is formed in a chiral environment, as depicted in Figure 8. Combination of the two radical centers from the *Re* face—resulting in the (5*S*) configuration in the product—is facile, whilst it is hampered from the *Si* face. Indeed, both major enantiomers, the *exo* product **12a** and the *endo* product **12b**, exhibit the (5*S*) configuration.[33]

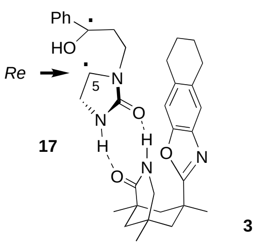
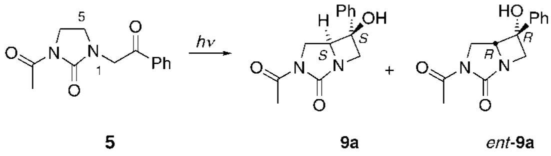


Figure 8. The 1,5-biradical **17** in the environment of the chiral host **3**.

The increased enantioselectivity at lower temperature arises from the stronger association between host and substrate. This equilibrium is further shifted towards the complex by the presence of an excess of the host. Unfortunately, association data in toluene could not be obtained, due to the limited solubility of substrate **8**. Still, it is evident that the sophisticated hosts **3** and *ent*-**3** facilitate association because of their almost planar hetarene unit, in comparison with the menthyl group in **1** and **2**. In addition, the tetrahydronaphthalene unit provides excessive steric bulk to effect suitable shielding. From the almost perfect enantiofacial differentiation observed in photocycloadditions in the presence of compound **3**,[22] we favor the notion that the incomplete facial differentiation in the photocyclization is due to incomplete association.

On comparing the enantiofacial differentiation for the two diastereoisomers **12b** and **12a**, no explanation for the decreased enantioselectivity is readily apparent, either from experimental data or from previous work. Sensible speculation on this issue has to include the nature of the transition state and the trajectory at which the two radical centers approach each other. A later transition state (i.e., a greater distance between the carbon centers) or an approach of the radical centers from the upper part of the bound imidazolidinone could both account for the decreased selectivity in the *endo* case.

Solid-state irradiation: Compound **5**, which crystallized in a chiral space group (see above), was irradiated in the solid state. A suitable homochiral crystal was selected by visual inspection of crystals in a polarization microscope. The crystal was powdered, and equal fractions of the powder were put in quartz tubes. Upon continued irradiation at $\lambda = 300$ nm (Rayonet RPR-3000 Å), the progress of the reaction was monitored by dilution of a single fraction in isopropanol and subsequent HPLC analysis (Scheme 6, Table 3).



Scheme 6. Enantioselective Norrish–Yang cyclization reaction of substrate **5** in the solid state.

Table 3. Enantioselectivities recorded for the Norrish–Yang cyclization of substrate **5** in the solid-state (cf. Scheme 6).

	t[a] [h]	Conv.[b] [%]	*exo*:*endo*	*ee*[c] [%]
1	0.5	1	94:6	78
2	1.0	2	90:10	62
3	2.0	5	90:10	54
4	4.0	20	89:11	41
5	14.0	29	87:13	32
6	24.0	36	87:13	28

[a] The reactions were carried out by irradiation in a quartz tube (irradiation source: Rayonet RPR-3000 Å). [b] Conversion of substrate **5** into cyclization products **9**. Acetophenone was also formed as a side product. [c] The enantiomeric excess of the major *exo* diastereoisomer **9a** was determined by HPLC (see Experimental Section).

At the beginning of the reaction, the enantiomeric excess was high (78% *ee*) at low conversion (entry 1). The selectivity decreased after prolonged irradiation. The last value recorded—after 24 h (entry 6)—was 28% *ee*. The phenomenon of a decrease in selectivity has precedent in enantioselective solid-state photochemical reactions and was attributed to increasing disorder in the crystal.[12d]

CD spectra of the photocyclization product revealed that the major product most probably had the *R* configuration at carbon atom C-6.[34] The assignment is based on the positive Cotton effect between 250 and 200 nm. The *exo* diastereoisomer was clearly preferred, irrespective of the irradiation time. Consequently, the major product is presumably *ent*-**9a**, with the (5*R*,6*R*) configuration. In turn, this means that we had by chance picked as irradiation precursor a crystal in which abstraction of the *pro-S* hydrogen atom at C-5 is facilitated, the structure of which is depicted in Figure 2. Attempts to obtain uniformly configured crystals by seeding were not successful.

Conclusion

Enantioselective Norrish–Yang cyclization of imidazolidinone-based substrates in solution is possible through employment of the chiral complexing agents **1**–**3**. These agents can bind to the substrates through two hydrogen bonds and provide a chiral environment in which the reaction occurs. Whereas the yield and simple diastereoselectivity remained unchanged in the presence of the complexing agent, significant enantioselectivity was observed (up to 60% *ee*). A further increase in the enantiomeric excess was impossible, presumably due to insufficient binding of the imidazolone substrate as compared to, for example, lactams. The experimental parameters were limited by the solubility of the substrate (temperature) and by practical considerations (excess of complexing agents). The enantioselective Norrish–Yang cyclization of compound **8** in solution can be compared to the analogous reaction of compound **5** in the solid state. In the latter case, the initial *ee* was high (78% *ee*), but it decreased in the course of the reaction. As a result, the enantiomeric excess after 24 h was only 28%.

Several extensions of the methodology described are conceivable and are currently being studied. Lactam substrates with an exclusive stereogenic center that is converted into a prostereogenic center by hydrogen abstraction can be converted into enantiomerically enriched products. Chiral spiro compounds would be accessible by these means. Radical reactions of lactams or imidazolidinones, which can be induced at low temperature and which may occur both intramolecularly or intermolecularly, are interesting test reactions. Other host compounds allowing an improved association would merit investigation. Three hydrogen bonds instead of two would be ideal to ensure sufficient bonding of the substrate to the chiral complexing agent. Work along these lines is currently being pursued in our laboratory and will be reported in due course.

Experimental Section

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Common solvents [pentane (P), diethyl ether, *tert*-butyl methyl ether (TBME), tetrahydrofuran (THF), dichloromethane, ethyl acetate (EtOAc), methanol] and acetic anhydride (Ac_2O) were distilled prior to use. Anhydrous CH_2Cl_2 was distilled from CaH_2, anhydrous Et_2O and THF from K/Na immediately prior to use. All other reagents and solvents were used as received. Irradiation experiments were performed in *t*BuOH (Acros p. a.) or toluene (Merck Uvasol) under Ar. TLC: Merck glass plates (0.25 mm silica gel 60, F_{254}), eluent given in brackets. Detection by UV or by coloration with ceric ammonium molybdate (CAM). Optical rotation: Perkin–Elmer 241 MC. HPLC: Dionex Pump P580A LPG, UV Detector UVD 340S. Columns: Daicel ChiralCel OD (250 × 4.60 mm, hexane/isopropanol 80:20, flow = 0.50 mL min^{-1}), Macherey–Nagel Nucleodex β-OH (200 × 4.00 mm, H_2O/MeCN 95:5 → 87:13 over 80 min, flow = 0.42 mL min^{-1}). Solvents: Merck LiChrosolv, detection wavelength given in brackets. Melting points (uncorrected): Reichert hot bench. NMR: Bruker ARX 200, AC 250, AC 300, and AX 500 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature unless stated otherwise. Chemical shifts are reported relative to tetramethylsilane as internal standard or to distinguished solvent signals. Apparent multiplets occurring as a result of accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). If there is a missing signal due to superimposition, the spectrum is marked with an asterisk (*). NOESY contacts are reported as weak (′), medium (″), or strong (‴). IR: Bruker IFS 200 or Perkin Elmer 1600 FT-IR. MS: Varian CH7 (EI) or Finnigan MAT 8200 (EI). HRMS: Finnigan MAT 8200 (EI). GC-MS: Agilent 6890 (GC system), Agilent 5973 (mass selective detector, EI), Column: HP 5MS (30 m). Elemental analysis: CHN: Elementar vario EL, CH: Mikroanalytical laboratory Beller. UV/Vis: Jasco V-550, ambient temperature. CD: Jasco J-715 CD Spectropolarimeter, 20 °C. Flash chromatography:[35] Merck silica gel 60 (230–400 mesh, ≈50 g for each 1 g of material to be separated), eluent given in brackets.

General procedure for the photochemical reactions of *N*-substituted imidazolidinones in the absence of a chiral host (GP A): Photochemical reactions were conducted in a merry-go-round apparatus (irradiation source: Rayonet RPR-3000 Å, quartz tubes) at approximately 35 °C. The substrates were dissolved in the given solvents and degassed for 30 min with a continuous stream of argon. The mixture was subsequently irradiated until the reaction was complete according to TLC (ca. 3 h). After evaporation of the solvent the residue was purified by flash chromatography.

General procedure for the photochemical reactions of *N*-substituted imidazolidinones with a chiral host (GP B): The reactions were conducted in a liquid-cooled merry-go-round apparatus (irradiation source: Original Hanau TQ 150, duran filter) at −45 °C. A solution of the substrate **8** ($c = 5.0 \times 10^{-3}$ mol L^{-1}) and the chiral host **1**, **2**, **3**, or *ent*-**3** ($c = 5.0 \times 10^{-3}$ or 12.5×10^{-3} mol L^{-1}) in toluene was degassed for 30 min with a continuous stream of argon. The mixture was subsequently irradiated until the reaction was complete according to TLC (12–20 h). After evaporation of the solvent, the diastereomeric ratio was determined from the crude product by integration of appropriate ^{1}H NMR signals. The residue was purified by flash chromatography. The collected fractions of the separated diastereoisomers were evaporated, and the enantiomeric excess was determined by chiral HPLC (*exo*: Nucleodex β-OH; *endo*: ChiralCel OD).

General procedure for the photochemical reaction of *N*-acetyl-*N′*-(2-oxo-2-phenylethyl)-imidazolidin-2-one (5) in the single-crystal state (GP C): A single homochiral crystal of compound **5** was powdered, and equal fractions (246 µg, 1.00 µmol) of the powder were put in quartz tubes. The samples were irradiated for different periods of time (Table 3) in a merry-go-round apparatus (irradiation source: Rayonet RPR-3000 Å) at approximately 35 °C. After the irradiation, the pale yellow solid was dissolved in isopropanol (246 µL) and the conversion, the diastereomeric ratio, and the enantiomeric excess was determined by chiral HPLC (ChiralCel OD).

***N*-Acetylimidazolidin-2-one (4)**:[23] Imidazolidin-2-one (20.0 g, 210 mmol, $C_3H_6N_2O \cdot 0.5\,H_2O$) was heated under reflux in Ac_2O (200 mL) for 30 min. The product partly precipitated during cooling. After filtration, the solid was washed with cold ethanol (20 mL). The solutions were combined, and the Ac_2O was removed by azeotropic distillation (EtOH) in vacuum. The resulting solid was purified by recrystallization (EtOH). Both fractions (23.7 g, 185 mmol, 88 %) were obtained as white solids. $R_f = 0.22$ (EtOAc); m.p. 177 – 178 °C; ^{1}H NMR (200 MHz): $\delta = 6.19$ (brs, 1H; NH), 3.96 (t, $^3J = 8.0$ Hz, 2H; CH_2), 3.51 (t, $^3J = 8.0$ Hz, 2H; CH_2), 2.50 (s, 3H; CH_3); ^{13}C NMR (50.3 MHz): $\delta = 170.8$ (CH_3CO), 157.0 (NCON), 42.1 (CH_2NAc), 36.4 (CH_2NH), 23.3 (CH_3CO).

***N*-Acetyl-*N′*-(2-oxo-2-phenylethyl)-imidazolidin-2-one (5)**:[24] Under argon, *N*-acetylimidazolidin-2-one (**4**, 640 mg, 5.00 mmol) was added to a stirred suspension of sodium hydride (132 mg, 5.50 mmol) in anhydrous THF (10 mL). After the mixture had been kept for 1 h at room temperature, potassium iodide (166 mg, 1.00 mmol) was added. The suspension was treated dropwise with a solution of phenacyl bromide (1.50 g, 7.50 mmol) in anhydrous THF (10 mL) and stirred for 20 h at 70 °C (oil bath temperature). After cooling, the suspension was filtered, and the residue was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. After chromatographic purification (TBME → EtOAc), compound **5** (491 mg, 40 %) was obtained as a white solid. $R_f = 0.20$ (TBME); $t_R = 42.60$ min (ChiralCel OD, 220 nm); m.p. 105 °C; ^{1}H NMR (200 MHz): $\delta = 8.02 - 7.90$ (m, 2H; arom. H), 7.68 – 7.42 (m, 3H; arom. H), 4.73 (s, 2H; CH_2CO), 3.93 (t, $^3J = 8.0$ Hz, 2H; CH_2NR), 3.57 (t, $^3J = 8.0$ Hz, 2H; CH_2NAc), 2.52 (s, 3H; CH_3); ^{13}C NMR (75.5 MHz): $\delta = 193.2$ (PhCO), 170.6 (CH_3CO), 155.3 (NCON), 134.5 (C_{ar}), 133.9 ($C_{ar}H$), 128.8 ($C_{ar}H$), 127.8 ($C_{ar}H$), 49.7 (CH_2CO), 41.6 (CH_2NAc), 39.6 (CH_2NR), 23.2 (CH_3CO); IR (KBr): $\tilde{\nu} = 3041$ (w; $C_{ar}H$), 2916 (m; $C_{al}H$), 1721 (vs; C=O), 1693 (vs; C=O), 1682 (vs; C=O), 1272 (s), 762 (s), 690 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 246 (3) $[M]^+$, 141 (55) $[M - \mathrm{PhCO}]^+$, 127 (49) $[M - \mathrm{PhCOCH_2}]^+$, 120 (60) $[\mathrm{PhCOCH_3}]^+$, 105 (84) $[\mathrm{PhCO}]^+$, 99 (100) $[M - \mathrm{PhCOCH_3} - \mathrm{HCN}]^+$, 77 (44) $[C_6H_5]^+$, 43 (74) $[CH_3CO]^+$; elemental analysis calcd (%) for $C_{13}H_{14}N_2O_3$ (246.26): C 63.40, H 5.73, N 11.38; found C 63.35, H 5.57, N 11.25.

***N*-(2-Oxo-2-phenylethyl)-imidazolidin-2-one (6)**: *N*-Acetyl-*N′*-(2-oxo-2-phenylethyl)-imidazolidin-2-one (**5**, 4.12 g, 16.7 mmol) was suspended in methanol (100 mL), treated with aqueous NaOH (4 N, 100 mL), and stirred for 2 h at 50 °C. The solvent was partly (ca. 100 mL) removed in vacuo and the residue was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. After chromatographic purification (EtOAc → EtOAc/MeOH 90:10), compound **6** (2.84 g, 83 %) was obtained as a white solid. $R_f = 0.10$ (EtOAc); m.p. 156 °C; ^{1}H NMR (500 MHz): $\delta = 8.02 - 7.97$ (m, 2H; arom. H), 7.61 – 7.57 (m, 1H; arom. H), 7.50 – 7.43 (m, 2H; arom. H), 4.95 (brs, 1H; NH), 4.64 (s, 2H; CH_2CO), 3.62 – 3.58 (m, 2H; CH_2NR), 3.54 – 3.49 (m, 2H; CH_2NH); ^{13}C NMR (50.3 MHz): $\delta = 194.8$ (PhCO), 162.8 (NCON), 135.0 (C_{ar}), 133.6 ($C_{ar}H$), 128.7 ($C_{ar}H$), 128.0 ($C_{ar}H$), 50.0 (CH_2CO), 45.6 (CH_2NR), 38.2 (CH_2NH); IR (KBr): $\tilde{\nu} = 3227$ (s, N–H), 3094 (m; $C_{ar}H$), 2837 (w; $C_{al}H$), 1703 (vs; C=O), 1690 (vs; C=O), 1285 (s), 1225 (s), 760 (s), 688 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 204 (23) $[M]^+$, 120 (21) $[\mathrm{PhCOCH_3}]^+$, 105 (51) $[\mathrm{PhCO}]^+$, 99 (100) $[M - \mathrm{PhCO}]^+$, 85 (69) $[M - \mathrm{PhCOCH_2}]^+$, 77 (58) $[C_6H_5]^+$, 56 (79); elemental analysis calcd (%) for $C_{13}H_{14}N_2O_3$ (204.23): C 64.69, H 5.92, N 13.72; found C 65.02, H 5.91, N 13.71.

***N*-Acetyl-*N′*-(3-oxo-3-phenylpropyl)-imidazolidin-2-one (7)**:[25] 3-Dimethylamino-1-phenylpropan-1-one hydrochloride (15.9 g, 74.2 mmol) and *N*-acetylimidazolidin-2-one (**4**, 19.0 g, 148 mmol) were suspended in *o*-xylene (100 mL) and heated for 6 h under reflux. Upon cooling, the solution was treated with water (200 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. After chromatographic purification (P/EtOAc 20:80 → EtOAc/MeOH 95:5) and recrystallisation (Et_2O/EtOAc), compound **7** (6.34 g, 33 %) was obtained as a white solid. $R_f = 0.36$ (EtOAc); m.p. 78 °C; ^{1}H NMR (300 MHz): $\delta = 8.00 - 7.92$ (m, 2H; arom. H), 7.62 – 7.53 (m, 1H; arom. H), 7.52 – 7.42 (m, 2H; arom. H), 3.80 (t, $^3J = 8.1$ Hz, 2H; CH_2NR), 3.71 (t, $^3J = 6.3$ Hz, 2H; NCH_2CH$_2$CO), 3.54 (t, $^3J = 8.1$ Hz, 2H; CH_2NAc), 3.32 (t, $^3J = 6.3$ Hz, 2H; NCH$_2$$CH_2$CO), 2.49 (s, 3H; CH_3); ^{13}C NMR (50.3 MHz): $\delta = 197.9$ (PhCO), 170.4 (CH_3CO), 154.8 (NCON), 136.2 (C_{ar}), 133.4 ($C_{ar}H$), 128.6 ($C_{ar}H$), 127.9 ($C_{ar}H$), 41.9 (CH_2NAc), 39.5 (CH_2NR), 39.0 (NCH_2CH$_2$CO), 36.5 (NCH$_2$$CH_2$CO), 23.1 ($CH_3$); IR (KBr): $\tilde{\nu} = 3065$ (w; $C_{ar}H$), 2976 (w; $C_{al}H$), 1722 (vs; C=O), 1671 (vs; C=O), 1265 (s), 750 (m), 691 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 260 (27) $[M]^+$, 155 (100) $[M - \mathrm{PhCO}]^+$, 105 (47) $[\mathrm{PhCO}]^+$; elemental analysis calcd (%) for $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20, N 10.76; found C 64.37, H 5.87, N 10.50.

***N*-(3-Oxo-3-phenylpropyl)-imidazolidin-2-one (8)**: *N*-Acetyl-*N′*-(3-oxo-3-phenylpropyl)-imidazolidin-2-one (**7**, 1.08 g, 4.16 mmol) was dissolved in methanol (25 mL), treated with aqueous NaOH (1 N, 25 mL), and stirred for 1.5 h at room temperature. Methanol was removed in vacuo, and the solution was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL). After drying over Na_2SO_4 and filtration, the solvent was removed in vacuo. After chromatographic purification (EtOAc → EtOAc/MeOH 90:10), compound **8** (719 mg, 79 %) was obtained as a white solid. $R_f = 0.46$ (EtOAc/MeOH 80:20); m.p. 122 °C; ^{1}H NMR (300 MHz): $\delta = 7.90 - 7.81$ (m, 2H; arom. H), 7.50 – 7.32 (m, 3H; arom. H), 5.47 (brs, 1H; NH), 3.54 (t, $^3J = 6.4$ Hz, 2H; NCH_2CH$_2$CO), 3.43 (t, $^3J = 8.1$ Hz, 2H; CH_2NR), 3.30 (t, $^3J = 8.1$ Hz, 2H; CH_2NH), 3.18 (t, $^3J = 6.4$ Hz, 2H; NCH$_2$$CH_2$CO); ^{13}C NMR (75.5 MHz): $\delta = 196.6$ (PhCO), 163.0 (NCON), 136.5 (C_{ar}), 133.2 ($C_{ar}H$), 128.5 ($C_{ar}H$), 127.9 ($C_{ar}H$), 46.1 (HNCH$_2$$CH_2$NR), 38.9 (N$CH_2CH_2$CO), 38.3 (HN$CH_2CH_2$NR), 37.2 (NCH$_2$$CH_2$CO); IR (KBr): $\tilde{\nu} = 3278$ (brs, NH), 2899 (w; $C_{al}H$), 1682 (vs; C=O), 1653 (vs; C=O), 1501 (s), 1281 (s), 747 (s), 690 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 218 (20) $[M]^+$, 113 (100) $[M - \mathrm{PhCO}]^+$, 105 (71) $[\mathrm{PhCO}]^+$, 99 (76) $[C_4H_7N_2O]^+$, 87 (49), 77 (40) $[C_6H_5]^+$; elemental analysis calcd (%) for $C_{12}H_{14}N_2O_2$ (218.25): C 66.04, H 6.47, N 12.84; found C 65.65, H 6.34, N 12.52.

3-Acetyl-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.2.0]heptan-2-one (*rac*-9a/9b): According to GP A, *N*-acetyl-*N′*-(2-oxo-2-phenylethyl)-imidazolidin-2-one (**5**, 246 mg, 1.00 mmol) was irradiated in *t*BuOH (40 mL). After chromatographic purification (P/TBME 60:40 → 20:80), compounds *rac*-**9a/9b** (162 mg, 66 %) were obtained as white solids.

***exo*-3-Acetyl-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.2.0]heptan-2-one (*rac*-9a)**: Yield 77.0 mg (31 %); $R_f = 0.46$ (TBME); $t_R = 24.10$, 33.40 min (ChiralCel OD, 220 nm); m.p. 190 °C; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.42 - 7.32$ (m, 4H; arom. H), 7.28 – 7.24 (m, 1H; arom. H), 4.68 (ddd, $^3J(\text{H-}4_\alpha) = 8.7$ Hz, $^3J(\text{H-}4_\beta) = 3.0$ Hz, $^4J(\text{H-}7_\beta) = 0.9$ Hz, 1H; H-5), 4.47 (d, $^2J = 10.6$ Hz, 1H; H-7_α), 4.16 (dd, $^2J = 11.8$ Hz, $^3J(\text{H-5}) = 3.0$ Hz, 1H; H-4_β), 3.89 (dd, $^2J = 10.6$ Hz, $^4J(\text{H-5}) = 0.9$ Hz, 1H; H-7_β), 3.85 (dd, $^2J = 11.8$ Hz, $^3J(\text{H-5}) = 8.7$ Hz, 1H; H-4_α), 2.41 (s, 3H; CH_3CO); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 173.1$ (CH_3CO), 166.0 (NCON), 143.2 (C_{ar}), 129.9 ($C_{ar}H$), 129.3 ($C_{ar}H$), 126.7 ($C_{ar}H$), 82.0 (C-6), 68.2 (C-7), 66.7 (C-5), 43.5 (C-4), 23.5 (CH_3CO); NOESY experiment: arom. H → H-5(″), arom. H → H-7_α(″); IR (KBr): $\tilde{\nu} = 3387$ (s; OH), 3027 (w; $C_{ar}H$), 2950 (m; $C_{al}H$), 1707 (vs; C=O), 1692 (vs; C=O), 1370 (s), 1304 (m), 1242 (m), 767 (m), 704 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 246 (<1) $[M]^+$, 141 (16), 127 (27) $[C_5H_7N_2O_2]^+$, 120 (100) $[\mathrm{PhCOCH_3}]^+$, 105 (37) $[\mathrm{PhCO}]^+$, 85 (40) $[C_3H_5N_2O]^+$, 78 (29), 43 (67) $[CH_3CO]^+$; elemental analysis calcd (%) for $C_{13}H_{14}N_2O_3$ (246.26): C 63.40, H 5.73; found C 63.19, H 5.77.

***endo*-3-Acetyl-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.2.0]heptan-2-one (*rac*-9b)**: Yield 85.0 mg (35 %); $R_f = 0.34$ (TBME); $t_R = 14.90$, 17.30 min (ChiralCel OD, 220 nm); m.p. 124 – 127 °C; ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.41 - 7.36$ (m, 4H; arom. H), 7.33 – 7.28 (m, 1H; arom. H), 4.60 (d, $^2J = 10.8$ Hz, 1H; H-7_β), 4.58 (dd, $^3J(\text{H-}4_\alpha) = 9.1$ Hz, $^3J(\text{H-}4_\beta) = 3.2$ Hz, 1H; H-5), 4.24 (d, $^2J = 10.8$ Hz, 1H; H-7_α), 3.65 (dd, $^2J = 12.4$ Hz,

^3J(H-5) = 9.1 Hz, 1H; H-4$_\alpha$), 3.02 (dd, ^2J = 12.4 Hz, ^3J(H-5) = 3.2 Hz, 1H; H-4$_\beta$), 2.24 (s, 3H; CH_3CO); ^{13}C NMR (75.5 MHz, CD_3OD): δ = 172.4 ($CH_3\mathit{C}O$), 164.4 (NCON), 139.2 (C_{ar}), 130.1 ($C_{ar}H$), 129.9 ($C_{ar}H$), 127.3 ($C_{ar}H$), 82.4 (C-6), 69.7 (C-5), 65.9 (C-7), 45.5 (C-4), 23.3 ($\mathit{C}H_3CO$); NOESY experiment: arom. H → H-7$_\beta$(″); IR (KBr): $\tilde{\nu}$ = 3385 (s; OH), 3058 (w; $C_{ar}H$), 2965 (m; $C_{al}H$), 1728 (vs; C=O), 1659 (vs; C=O), 1354 (vs), 759 (m), 700 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 246 (<1) $[M]^+$, 141 (8), 127 (24) $[C_5H_7N_2O_2]^+$, 120 (100) $[PhCOCH_3]^+$, 105 (46) $[PhCO]^+$, 85 (66) $[C_3H_5N_2O]^+$, 78 (43), 43 (55) $[CH_3CO]^+$; elemental analysis calcd (%) for $C_{13}H_{14}N_2O_3$ (246.26): C 63.40, H 5.73; found C 63.16, H 5.73.

6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.2.0]heptan-2-one (*rac*-10a/10b): According to GP A, *N*-(2-oxo-2-phenylethyl)-imidazolidin-2-one (**6**, 204 mg, 1.00 mmol) was irradiated in *t*BuOH (40 mL). After chromatographic purification (EtOAc/MeOH 98:2), compounds *rac*-**10a/10b** (105 mg, 51%) were obtained as white solids.

***exo*-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.2.0]heptan-2-one (*rac*-10a)**: Yield 55.0 mg (27%); R_f = 0.52 (EE/MeOH 80:20); m.p. 238–240 °C; ^{1}H NMR (200 MHz, $[D_6]$DMSO): δ = 7.49–7.21 (m, 5H; arom. H), 7.10 (brs, 1H; NH), 4.55 (dd, ^3J(H-4$_\alpha$) = 9.0 Hz, ^3J(H-4$_\beta$) = 2.8 Hz, 1H; H-5), 4.12 (d, ^2J = 10.0 Hz, 1H; H-7$_\alpha$), 3.76–3.62 (m, 2H; H-4$_\beta$, H-7$_\beta$), 3.58–3.28 (brs, 1H; OH), 3.34 (virt. t, $^2J \approx {}^3J$(H-5) = 9.0 Hz, 1H; H-4$_\alpha$); ^{13}C NMR (75.5 MHz, CD_3OD): δ = 169.6 (NCON), 143.9 (C_{ar}), 128.4 ($C_{ar}H$), 127.4 ($C_{ar}H$), 125.3 ($C_{ar}H$), 78.4 (C-6), 68.5 (C-5), 65.5 (C-7), 38.9 (C-4); NOESY experiment: arom. H → H-5(″), arom. H → H-7$_\alpha$(″); IR (KBr): $\tilde{\nu}$ = 3270 (s), 3205 (br m), 3027 (w; $C_{ar}H$), 2956 (m; $C_{al}H$), 1671 (vs; C=O), 703 (s), 690 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 204 (<1) $[M]^+$, 120 (56) $[PhCOCH_3]^+$, 105 (51) $[PhCO]^+$, 99 (30), 85 (100) $[C_3H_5N_2O]^+$, 77 (37) $[C_6H_5]^+$; elemental analysis calcd (%) for $C_{13}H_{14}N_2O_3$ (204.23): C 64.69, H 5.92, N 13.72; found C 64.40, H 6.14, N 13.65.

***endo*-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.2.0]heptan-2-one (*rac*-10b)**: Yield 50.0 mg (24%); R_f = 0.58 (EtOAc/MeOH 80:20); m.p. 175 °C; ^{1}H NMR (200 MHz, CD_3OD): δ = 7.47–7.15 (m, 5H; arom. H), 4.58 (dd, ^3J(H-4$_\alpha$) = 9.0 Hz, ^3J(H-4$_\beta$) = 2.6 Hz, 1H; H-5), 4.45 (d, ^2J = 10.9 Hz, 1H; H-7$_\beta$), 4.06 (d, ^2J = 10.9 Hz, 1H; H-7$_\alpha$), 3.30 (dd, ^2J = 10.3 Hz, ^3J(H-5) = 9.0 Hz, 1H; H-4$_\alpha$), 2.67 (dd, ^2J = 10.3 Hz, ^3J(H-5) = 2.6 Hz, 1H; H-4$_\beta$); ^{13}C NMR (75.5 MHz, CD_3OD): δ = 171.8 (NCON), 140.4 (C_{ar}), 129.8 ($C_{ar}H$), 129.5 ($C_{ar}H$), 127.6 ($C_{ar}H$), 82.1 (C-6), 74.1 (C-5), 65.5 (C-7), 42.9 (C-4); NOESY experiment: arom. H → H-7$_\beta$(″); IR (KBr): $\tilde{\nu}$ = 3260 (s), 3133 (br m), 3021 (w; $C_{ar}H$), 2968 (m; $C_{al}H$), 1673 (vs; C=O), 758 (m), 696 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 204 (<1) $[M]^+$, 120 (56) $[PhCOCH_3]^+$, 105 (62) $[PhCO]^+$, 99 (15), 85 (100) $[C_3H_5N_2O]^+$, 77 (29) $[C_6H_5]^+$; elemental analysis calcd (%) for $C_{13}H_{14}N_2O_3$ (204.23): C 64.69, H 5.92, N 13.72; found C 64.54, H 5.81, N 13.55.

3-Acetyl-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-11a/11b): According to GP A, *N*-acetyl-*N*′-(3-oxo-3-phenylpropyl)-imidazolidin-2-one (**7**, 52.0 mg, 0.20 mmol) was irradiated in toluene (40 mL). After chromatographic purification (Et_2O), compounds *rac*-**11a/11b** (29.0 mg, 55%) were obtained as white solids.

***exo*-3-Acetyl-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-11a)**: Yield 21.0 mg (40%); R_f = 0.50 (EtOAc); m.p. 128 °C; ^{1}H NMR (250 MHz): δ = 7.47–7.27 (m, 5H; arom. H), 4.01–3.63 (m, 4H), 3.51–3.37 (m, 1H), 2.90 (brs, 1H; OH), 2.41 (s, 3H; CH_3CO), 2.61–2.26 (m, 2H); ^{13}C NMR (62.9 MHz): δ = 170.8 ($CH_3\mathit{C}O$), 158.5 (NCON), 140.2 (C_{ar}), 128.8 ($C_{ar}H$), 128.1 ($C_{ar}H$), 125.2 ($C_{ar}H$), 79.6 (C_{al}), 63.6 (CH), 43.6 (CH_2), 40.7 (CH_2), 40.4 (CH_2), 23.3 ($\mathit{C}H_3CO$); IR (KBr): $\tilde{\nu}$ = 3346 (s; O–H), 1749 (vs; C=O), 1637 (vs; C=O), 1376 (vs), 757 (m), 698 cm^{-1} (m); GC-MS (EI, 70 eV, t_R = 23.35 min): m/z (%): 260 (12) $[M]^+$, 155 (100) $[M - PhCO]^+$, 105 (31) $[PhCO]^+$, 98 (49) $[C_4H_6N_2O]^+$, 85 (22) $[C_3H_5N_2O]^+$; elemental analysis calcd (%) for $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20; found C 64.51, H 5.96.

***endo*-3-Acetyl-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-11b)**: Yield 8.00 mg (15%); R_f = 0.40 (EtOAc); m.p. 119 °C; ^{1}H NMR (250 MHz): δ = 7.42–7.23 (m, 5H; arom. H), 4.11–3.93 (m, 2H), 3.73–3.44 (m, 2H), 3.22 (dd, ^2J = 12.2 Hz, ^3J = 4.3 Hz, 1H), 2.79 (brs, 1H; OH), 2.63–2.49 (m, 1H), 2.38–2.26 (m, 1H), 2.20 (s, 3H; CH_3CO); ^{13}C NMR (62.9 MHz): δ = 170.1 ($CH_3\mathit{C}O$), 156.9 (NCON), 140.9 (C_{ar}), 128.7 ($C_{ar}H$), 128.5 ($C_{ar}H$), 125.4 ($C_{ar}H$), 81.5 (C_{al}), 63.6 (CH), 44.5 (CH_2), 42.6 (CH_2), 40.6 (CH_2), 22.9 ($\mathit{C}H_3CO$); IR (KBr): $\tilde{\nu}$ = 3383 (s; O–H), 1685 (vs, b; C=O), 1375 (s), 756 (s), 703 cm^{-1} (s); GC-MS (EI, 70 eV, t_R = 21.78 min): m/z (%): 260 (14) $[M]^+$, 155 (100) $[M - PhCO]^+$, 105 (25) $[PhCO]^+$, 98 (45) $[C_4H_6N_2O]^+$, 85 (18) $[C_3H_5N_2O]^+$; HRMS (EI, 70 eV): calcd for $C_{14}H_{16}N_2O_3$: 260.1161; found 260.1161.

6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-12a/12b): According to GP A, *N*-(3-oxo-3-phenylpropyl)-imidazolidin-2-one (**8**, 110 mg, 0.50 mmol) was irradiated in *t*BuOH (20 mL). After chromatographic purification (EtOAc/MeOH 98:2), compounds *rac*-**12a/12b** (82 mg, 75%) were obtained as white solids.

***exo*-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-12a)**: Yield 32.0 mg (29%); R_f = 0.50 (EtOAc/MeOH 80:20); t_R = 76.32, 80.70 min (Nucleodex β-OH, 215 nm); m.p. 195–198 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 7.51–7.45 (m, 1H; arom. H), 7.36–7.31 (m, 2H; arom. H), 7.28–7.22 (m, 1H; arom. H), 4.11 (dd, ^3J(H-4$_\alpha$) = 9.5 Hz, ^3J(H-4$_\beta$) = 3.6 Hz, 1H; H-5), 3.65 (virt. dt, $^2J \approx {}^3J$(H-7$_\alpha$) = 10.3 Hz, ^3J(H-7$_\beta$) = 7.7 Hz, 1H; H-8$_\beta$), 3.52 (dd, ^2J = 9.5 Hz, ^3J(H-5) = 3.6 Hz, 1H; H-4$_\beta$), 3.39 (virt. t, $^2J \approx {}^3J$(H-5) = 9.5 Hz, 1H; H-4$_\alpha$), 3.32 (ddd, ^2J = 10.3 Hz, ^3J(H-7$_\alpha$) = 9.9 Hz, ^3J(H-7$_\beta$) = 1.4 Hz, 1H; H-8$_\alpha$), 2.45 (virt. dt, ^2J = 13.6 Hz, ^3J(H-8$_\alpha$) ≈ ^3J(H-8$_\beta$) = 9.9 Hz, 1H; H-7$_\alpha$), 2.24 (ddd, ^2J = 13.6 Hz, ^3J(H-8$_\beta$) = 7.7 Hz, ^3J(H-8$_\alpha$) = 1.4 Hz, 1H; H-7$_\beta$); ^{13}C NMR (50.3 MHz, CD_3OD): δ = 168.9 (NCON), 143.6 (C_{ar}), 129.7 ($C_{ar}H$), 128.6 ($C_{ar}H$), 126.9 ($C_{ar}H$), 80.9 (C-6), 70.2 (C-5), 45.2 (C-8), 42.3 (C-7), 39.3 (C-4); NOESY experiment: arom. H → H-5(″), arom. H → H-4$_\beta$(′), arom. H → H-7$_\alpha$(′); IR (KBr): $\tilde{\nu}$ = 3310 (s), 3057 (w; $C_{ar}H$), 2894 (m; $C_{al}H$), 2460 (s), 1668 (vs; C=O), 1490 (s), 1434 (s), 757 (m), 704 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 218 (21) $[M]^+$, 113 (67), 98 (100) $[C_4H_6N_2O]^+$, 85 (71) $[C_3H_5N_2O]^+$, 55 (96), 28 (63); elemental analysis calcd (%) for $C_{12}H_{14}N_2O_2$ (218.25): C 66.04, H 6.47, N 12.84; found C 65.95, H 6.68, N 12.50.

***endo*-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-12b)**: Yield 50.0 mg (46%); R_f = 0.52 (EtOAc/MeOH 80:20); t_R = 20.33, 25.17 min (ChiralCel OD, 220 nm), m.p. 170 °C; ^{1}H NMR (500 MHz, CD_3OD): δ = 7.33–7.39 (m, 4H; arom. H), 7.25–7.30 (m, 1H; arom. H), 3.99 (dd, ^3J(H-4$_\alpha$) = 9.4 Hz, ^3J(H-4$_\beta$) = 4.0 Hz, 1H; H-5), 3.84 (virt. sept, ^2J = 12.0 Hz, ^3J(H-7$_\beta$) = 7.9 Hz, ^3J(H-7$_\alpha$) = 4.3 Hz, 1H; H-8$_\beta$), 3.37 (virt. dt, ^2J = 12.0 Hz, ^3J(H-7$_\alpha$) ≈ ^3J(H-7$_\beta$) = 7.9 Hz, 1H; H-8$_\alpha$), 3.31 (dd, ^2J = 10.1 Hz, ^3J(H-5) = 9.4 Hz, 1H; H-4$_\alpha$), 2.70 (dd, ^2J = 10.1 Hz, ^3J(H-5) = 4.0 Hz, 1H; H-4$_\beta$), 2.37 (virt. dt, ^2J = 13.1 Hz, ^3J(H-8$_\alpha$) ≈ ^3J(H-8$_\beta$) = 7.9 Hz, 1H; H-7$_\beta$), 2.17 (virt. sept, ^2J = 13.1 Hz, ^3J(H-8$_\alpha$) = 7.9 Hz, ^3J(H-8$_\beta$) = 4.3 Hz, 1H; H-7$_\alpha$); ^{13}C NMR (75.5 MHz, CD_3OD): δ = 167.4 (NCON), 144.4 (C_{ar}), 129.6 ($C_{ar}H$), 128.8 ($C_{ar}H$), 127.4 ($C_{ar}H$), 83.7 (C-6), 70.8 (C-5), 46.3 (C-8), 42.1 (C-4), 41.8 (C-7); NOESY experiment: arom. H → H-8$_\beta$(″), arom. H → H-4$_\beta$(″), arom. H → H-7$_\beta$(″); IR (KBr): $\tilde{\nu}$ = 3323 (s), 3052 (w; $C_{ar}H$), 2899 (m; $C_{al}H$), 2474 (s), 1667 (vs; C=O), 1482 (s), 1446 (s), 761 (s), 701 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 218 (22) $[M]^+$, 113 (74), 98 (83) $[C_4H_6N_2O]^+$, 85 (57) $[C_3H_5N_2O]^+$, 55 (100), 28 (79); elemental analysis calcd (%) for $C_{12}H_{14}N_2O_2$ (218.25): C 66.04, H 6.47, N 12.84; found C 65.79, H 6.50, N 12.70.

***exo*-6-Phenyl-6-[(triethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-13)**: A solution of *exo*-3-acetyl-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-**11a**, 521 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with 2,6-lutidine (686 mg, 746 μL, 6.40 mmol) and cooled to 0 °C. With a syringe pump, triethylsilyl triflate (1.59 g, 1.36 mL, 6.00 mmol) was added dropwise to the stirred solution over a period of 1 h. After 4 h at 0 °C, the solution was allowed to warm to room temperature over 14 h. Saturated $NaHCO_3$ solution (20 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The resulting yellow oil was dissolved in methanol (5 mL), treated with K_2CO_3 (415 mg, 3.00 mmol), and stirred for 3 h at room temperature. Methanol was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. After chromatographic purification (P/EtOAc 80:20 → P/EtOAc 30:70), compound *rac*-**13** (363 mg, 55%) was obtained as a white solid. R_f = 0.08 (P/EtOAc 50:50); m.p. 117 °C; ^{1}H NMR (250 MHz): δ = 7.40–7.27 (m, 5H; arom. H), 4.94 (brs, 1H; NH), 3.88–3.65 (m, 3H), 3.54–3.32 (m, 2H), 2.61 (virt. dt, ^2J = 13.6 Hz, $^3J \approx {}^3J$ = 9.9 Hz, 1H), 2.38 (ddd, ^2J = 13.6 Hz, ^3J = 7.4 Hz, ^3J = 1.3 Hz, 1H), 0.82 [t, ^3J = 7.9 Hz, 9H; $Si(CH_2\mathit{C}\mathit{H}_3)_3$], 0.56–0.31 [m, 6H; $Si(\mathit{C}\mathit{H}_2CH_3)_3$]; ^{13}C NMR (62.9 MHz): δ = 165.3 (NCON), 141.5 (C_{ar}), 128.5 ($C_{ar}H$), 128.0 ($C_{ar}H$), 125.9 ($C_{ar}H$), 81.9 (C_{al}), 70.2 (CH), 45.2 (CH_2), 42.3 (CH_2), 39.3 (CH_2), 6.9

[Si(CH_2CH_3)$_3$], 6.2 [Si(CH_2CH_3)$_3$]; IR (KBr): $\tilde{\nu} = 3244$ (m; N–H), 2958 (m; $C_{al}H$), 2915 (m; $C_{al}H$), 1697 (vs; C=O), 1034 (m), 726 (m), 701 cm^{-1} (m); GC-MS (EI, 70 eV): m/z (%): 332 (3) $[M]^+$, 303 (100) $[M - C_2H_5]^+$, 274 (2), 245 (1), 98 (89) $[C_4H_6N_2O]^+$; elemental analysis calcd (%) for $C_{18}H_{28}N_2O_2Si$ (332.51): C 65.02, H 8.49; found C 65.36, H 8.62.

***exo*-3-((*R*)-Methoxyphenylacetyl)-6-phenyl-6-[(triethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (14/14′)**:[30] A stirred solution of *exo*-6-phenyl-6-[(triethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-**13**, 120 mg, 0.36 mmol) in anhydrous THF (4 mL) was cooled to −78 °C and treated with LHMDS (1 M in THF, 430 µL, 0.43 mmol). After 15 min, (*R*)-*O*-methylmandelic chloride[29] (160 mg, 0.86 mmol), dissolved in anhydrous THF (1 mL) and cooled to −78 °C, was added rapidly, and the solution was allowed to warm to room temperature over 2 h. CH_2Cl_2 (10 mL) was added, and the resulting solution was washed with aqueous HCl (0.1 N, 5 mL). The aqueous solution was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo. After chromatographic purification (P/Et_2O 60:40), compounds **14/14′** (135 mg, 78%) were obtained as white solids.

***exo*-(5*S*,6*R*)-3-((*R*)-Methoxyphenylacetyl)-6-phenyl-6-[(triethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (14)**: Yield 68.0 mg (39%); $R_f = 0.44$ (Et_2O); m.p. 104 °C; ^1H NMR (250 MHz): $\delta = 7.70 - 7.55$ (m, 2H; arom. H), 7.40 – 7.23 (m, 8H; arom. H), 6.10 (s, 1H; $CHOCH_3$), 4.08 (dd, $^2J = 11.7$ Hz, $^3J = 3.4$ Hz, 1H), 3.88 (dd, $^2J = 11.7$ Hz, $^3J = 9.2$ Hz, 1H), 3.77 – 3.60 (m, 2H), 3.41 (virt. t, $^2J \approx {}^3J = 10.4$ Hz, 1H), 3.31 (s, 3H; OCH_3), 2.64 (virt. dt, $^2J = 13.7$ Hz, $^3J \approx {}^3J = 9.9$ Hz, 1H), 2.34 (br dd, $^2J = 13.7$ Hz, $^3J = 6.7$ Hz, 1H), 0.52 [t, $^3J = 7.9$ Hz, 9H; Si(CH_2CH_3)$_3$], 0.11 [q, $^3J = 7.9$ Hz, 6H; Si(CH_2CH_3)$_3$]; ^{13}C NMR (62.9 MHz): $\delta = 170.5$ (CO), 157.2 (NCON), 140.3 (C_{ar}), 136.2 (C_{ar}), 128.8 ($C_{ar}H$), 128.6 ($C_{ar}H$), 128.4 ($C_{ar}H$), 128.3 ($C_{ar}H$), 128.2 ($C_{ar}H$), 125.8 ($C_{ar}H$), 81.2 (C_{al}), 80.4 ($CHOCH_3$), 65.7 (CH), 56.9 (CH_3O), 43.3 (CH_2), 41.2 (CH_2), 37.4 (CH_2), 6.6 [Si(CH_2CH_3)$_3$], 5.8 [Si(CH_2CH_3)$_3$]; IR (KBr): $\tilde{\nu} = 2953$ (m; $C_{al}H$), 1733 (vs; C=O), 1690 (vs; C=O), 1383 (vs), 746 (m), 696 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 480 (48) $[M]^+$, 451 (6) $[M - C_2H_5]^+$, 331 (1) $[M - C_9H_9O_2]^+$, 121 (100) $[C_8H_9O]^+$; HRMS (EI, 70 eV): calcd for $C_{27}H_{36}N_2O_4Si$: 480.2445; found 480.2440.

***exo*-(5*R*,6*S*)-3-((*R*)-Methoxyphenylacetyl)-6-phenyl-6-[(triethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (14′)**: Yield 67.0 mg (39%); $R_f = 0.68$ (Et_2O); m.p. 100 °C; ^1H NMR (250 MHz): $\delta = 7.56 - 7.48$ (m, 2H; arom. H), 7.37 – 7.23 (m, 8H; arom. H), 6.22 (s, 1H; $CHOCH_3$), 4.31 (dd, $^2J = 10.8$ Hz, $^3J = 3.2$ Hz, 1H), 3.84 – 3.56 (m, 3H), 3.38 (s, 3H; OCH_3), 3.45 – 3.27 (m, 1H), 2.59 (virt. dt, $^2J = 13.7$ Hz, $^3J \approx {}^3J = 9.8$ Hz, 1H), 2.49 – 2.36 (m, 1H), 0.80 [t, $^3J = 7.9$ Hz, 9H; Si(CH_2CH_3)$_3$], 0.48 – 0.33 [m, 6H; Si(CH_2CH_3)$_3$]; ^{13}C NMR (62.9 MHz): $\delta = 170.7$ (CO), 157.3 (NCON), 140.1 (C_{ar}), 136.7 (C_{ar}), 128.7 ($C_{ar}H$), 128.5 ($C_{ar}H$), 128.5 ($C_{ar}H$), 128.4 ($C_{ar}H$), 128.4 ($C_{ar}H$), 126.0 ($C_{ar}H$), 81.4 (C_{al}), 80.6 ($CHOCH_3$), 65.4 (CH), 57.2 (CH_3O), 43.1 (CH_2), 41.4 (CH_2), 37.6 (CH_2), 6.8 [Si(CH_2CH_3)$_3$], 6.1 [Si(CH_2CH_3)$_3$]; IR (KBr): $\tilde{\nu} = 2954$ (m; $C_{al}H$), 1718 (vs; C=O), 1684 (vs; C=O), 1385 (vs), 735 cm^{-1} (s); MS (EI, 70 eV): m/z (%): 480 (57) $[M]^+$, 451 (9) $[M - C_2H_5]^+$, 331 (5) $[M - C_9H_9O_2]^+$, 121 (100) $[C_8H_9O]^+$; HRMS (EI, 70 eV): calcd for $C_{27}H_{36}N_2O_4Si$: 480.2445; found 480.2442.

***exo*-(5*S*,6*R*)-6-Hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (15a)**: A solution of *exo*-(5*S*,6*R*)-3-((*R*)-methoxyphenylacetyl)-6-phenyl-6-[(triethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (**14**, 58 mg, 0.12 mmol) in anhydrous THF (1 mL) was treated with TBAF solution (1 M in THF, 130 µL, 0.13 mmol) and stirred for 1.5 h at room temperature. Silica gel (250 mg) was added and the solvent was removed in vacuo. After chromatographic purification (Et_2O), compound **15a** (39.0 mg, 89%) was obtained as a white solid. $R_f = 0.31$ (Et_2O); m.p. 157 °C; ^1H NMR (250 MHz): $\delta = 7.58 - 7.48$ (m, 2H; arom. H), 7.41 – 7.24 (m, 8H; arom. H), 6.06 (s, 1H; $CHOCH_3$), 3.92 (dd, $^3J = 8.4$ Hz, $^3J = 3.8$ Hz, 1H), 3.88 – 3.67 (m, 3H), 3.47 – 3.34 (m, 1H), 3.31 (s, 3H; OCH_3), 2.46 (virt. dt, $^2J = 13.8$ Hz, $^3J \approx {}^3J = 9.6$ Hz, 1H), 2.32 – 2.15 (m, 2H), 1.69 (br s, OH); ^{13}C NMR (62.9 MHz): $\delta = 170.2$ (CO), 157.7 (NCON), 140.0 (C_{ar}), 136.4 (C_{ar}), 128.8 ($C_{ar}H$), 128.3 ($C_{ar}H$), 128.2 ($C_{ar}H$), 128.1 ($C_{ar}H$), 125.1 ($C_{ar}H$), 80.2 (C_{al}), 79.4 ($CHOCH_3$), 64.0 (CH), 57.1 (CH_3O), 43.6 (CH_2), 40.6 (CH_2), 40.6 (CH_2); IR (KBr): $\tilde{\nu} = 3383$ (s; O–H), 1718 (vs; C=O), 1685 (vs; C=O), 1385 (vs), 750 (m), 698 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 366 (22) $[M]^+$, 217 (9) $[M - C_9H_9O_2]^+$, 121 (100) $[C_8H_9O]^+$, 105 (24) $[PhCO]^+$, 77 (14) $[C_6H_5]^+$; HRMS (EI, 70 eV): calcd for $C_{21}H_{22}N_2O_4$: 366.1580; found 366.1578.

***exo*-(5*R*,6*S*)-6-Hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (15a′)**: According to the procedure described for the transformation **14** → **15a**, a solution of *exo*-(5*R*,6*S*)-3-((*R*)-methoxyphenylacetyl)-6-phenyl-6-[(triethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (**14′**, 57 mg, 0.12 mmol) in anhydrous THF (1 mL) was treated with TBAF solution (1 M in THF, 130 µL, 0.13 mmol). After chromatographic purification (Et_2O), compound **15a′** (38.0 mg, 86%) was obtained as a white solid. $R_f = 0.30$ (Et_2O); m.p. 85 °C; ^1H NMR (250 MHz): $\delta = 7.54 - 7.45$ (m, 2H; arom. H), 7.44 – 7.27 (m, 8H; arom. H), 6.22 (s, 1H; $CHOCH_3$), 4.11 (dd, $^2J = 11.9$ Hz, $^3J = 3.5$ Hz, 1H), 3.93 – 3.74 (m, 2H), 3.61 (dd, $^2J = 11.9$ Hz, $^3J = 9.2$ Hz, 1H), 3.35 (s, 3H; OCH_3), 3.49 – 3.28 (m, 1H), 2.62 – 2.23 (m, 3H), 1.70 (br s; OH); ^{13}C NMR (62.9 MHz)*: $\delta = 170.9$ (CO), 157.6 (NCON), 140.0 (C_{ar}), 136.4 (C_{ar}), 128.9 ($C_{ar}H$), 128.6 ($C_{ar}H$), 128.5 ($C_{ar}H$), 128.3 ($C_{ar}H$), 125.2 ($C_{ar}H$), 80.5 (C_{al}), 79.7 ($CHOCH_3$), 63.8 (CH), 57.0 (CH_3O), 43.5 (CH_2), 40.7 (CH_2); IR (KBr): $\tilde{\nu} = 3446$ (m; O–H), 1734 (vs; C=O), 1678 (vs; C=O), 1384 (vs), 699 cm^{-1} (m); MS (EI, 70 eV): m/z (%): 366 (25) $[M]^+$, 217 (9) $[M - C_9H_9O_2]^+$, 121 (100) $[C_8H_9O]^+$, 105 (24) $[PhCO]^+$, 77 (14) $[C_6H_5]^+$; HRMS (EI, 70 eV): calcd for $C_{21}H_{22}N_2O_4$: 366.1580; found 366.1579.

***exo*-(5*S*,6*R*)-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (12a)**: *exo*-(5*S*,6*R*)-6-Hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (**15a**, 22.0 mg, 0.06 mmol) was dissolved in methanol (3 mL) and treated with K_2CO_3 (12.4 mg, 0.09 mmol). After 2.5 h stirring at room temperature, silica gel (300 mg) was added and the solvent was removed in vacuo. After chromatographic purification (EtOAc/MeOH 98:2), compound **12a** (11.0 mg, 84%) was obtained as a white solid. $[\alpha]_D^{20} = -50.2$ ($c = 0.6$ in MeOH); $t_R = 80.70$ min (Nucleodex β-OH, 215 nm).

***exo*-(5*R*,6*S*)-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*ent*-12a)**: According to the procedure described for the transformation **15a** → **12a**, *exo*-(5*R*,6*S*)-6-hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (**15a′**, 25.0 mg, 0.07 mmol) was dissolved in methanol (3 mL) and treated with K_2CO_3 (14.5 mg, 0.11 mmol). After chromatographic purification (EtOAc/MeOH 98:2), *ent*-**12a** (13.0 mg, 85%) was obtained as a white solid. $[\alpha]_D^{20} = +48.7$ ($c = 0.7$ in MeOH); $t_R = 76.32$ min (Nucleodex β-OH, 215 nm).

***endo*-6-Phenyl-6-[(trimethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-16)**: Imidazole (102 mg, 1.50 mmol) was added to a solution of *endo*-6-hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-**12b**, 218 mg, 1.00 mmol) in DMF (5 mL). The solution was cooled to 0 °C, and trimethylsilyl chloride (166 µL, 1.30 mmol) was slowly added. After 3.5 h stirring at 0 °C, the reaction was stopped by the addition of water (50 mL). The resulting solution was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and filtered. The solvent was removed in vacuo. After chromatographic purification (Et_2O → Et_2O/EtOAc 50:50), compound *rac*-**16** (211 mg, 73%) was obtained as a white solid. $R_f = 0.30$ (EtOAc); m.p. 153 °C; ^1H NMR (250 MHz): $\delta = 7.26 - 6.96$ (m, 5H; arom. H), 4.22 (br s, 1H; NH), 4.04 (dd, $^3J = 9.0$ Hz, $^3J = 1.3$ Hz, 1H), 3.95 – 3.83 (m, 1H), 3.44 – 3.22 (m, 2H), 2.70 (ddd, $^2J = 9.8$ Hz, $^3J = 4.2$ Hz, $^3J = 1.3$ Hz, 1H), 2.46 – 2.15 (m, 2H), −0.08 [s, 9H; Si(CH_3)$_3$]; ^{13}C NMR (62.9 MHz): $\delta = 164.6$ (NCON), 142.1 (C_{ar}), 128.2 ($C_{ar}H$), 127.7 ($C_{ar}H$), 126.2 ($C_{ar}H$), 84.7 (C_{al}), 70.7 (CH), 45.1 (CH_2), 40.9 (CH_2), 38.9 (CH_2), 1.8 [Si(CH_3)$_3$]; IR (KBr): $\tilde{\nu} = 3225$ (s; N–H), 2862 (m; $C_{al}H$), 1724 (vs; C=O), 1137 (s), 835 cm^{-1} (s); GC-MS (EI, 70 eV, $t_R = 21.58$ min): m/z (%): 290 (19) $[M]^+$, 275 (6) $[M - CH_3]^+$, 205 (41), 98 (100) $[C_4H_6N_2O]^+$; elemental analysis calcd (%) for $C_{15}H_{22}N_2O_2Si$ (290.43): C 62.03, H 7.64; found C 62.07, H 7.78.

***endo*-6-Hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo-[3.3.0]octane (15b/15b′)**: According to the procedure described for the transformation *rac*-**13** → **14/14′**, *endo*-6-phenyl-6-[(trimethylsilyl)oxy]-1,3-diazabicyclo[3.3.0]octan-2-one (*rac*-**16**, 261 mg, 0.90 mmol) in anhydrous THF (10 mL) was treated with LHMDS (1 M in THF, 1.10 mL, 1.10 mmol) and (*R*)-*O*-methylmandelic chloride (399 mg, 2.16 mmol, dissolved in 2 mL anhydrous THF). After workup, the crude product was obtained as a colorless oil. The oil was dissolved in anhydrous THF (5 mL) and treated with TBAF solution (1 M in THF, 1.00 mL, 1.00 mmol). After the mixture had been stirred for 2 h at room temperature, silica gel (1.00 g) was added and the solvent was removed in vacuo. After chromatographic purification (Et_2O), compounds **15b/15b′** (261 mg, 79%, d.r. 1:2) were obtained as white solids. The separation was not fully complete. A fraction containing both diastereoisomers was isolated (70.0 mg, 21%).

***endo*-(5*S*,6*S*)-6-Hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (15b)**: Yield 50.0 mg (15%); $R_f = 0.12$ (Et_2O); m.p. 46 °C (lyophilized from H_2O); ^1H NMR (250 MHz): $\delta = 7.33-7.21$ (m, 5H; arom. H), 7.02–6.83 (m, 5H; arom. H), 5.81 (s, 1H; C*H*OCH$_3$), 4.00–3.83 (m, 2H), 3.73 (dd, $^3J = 12.4$ Hz, $^3J = 9.0$ Hz, 1H), 3.58–3.40 (m, 1H), 3.19 (s, 3H; OCH_3), 3.07 (dd, $^3J = 12.4$ Hz, $^3J = 3.4$ Hz, 1H), 2.50–2.36 (m, 1H), 2.31–2.17 (m, 1H), 2.12 (s, 1H; OH); ^{13}C NMR (62.9 MHz)*: $\delta =$ 170.1 (CO), 156.0 (NCON), 140.5 (C_{ar}), 136.0 (C_{ar}), 128.7 ($C_{ar}H$), 128.4 ($C_{ar}H$), 128.3 ($C_{ar}H$), 128.2 ($C_{ar}H$), 124.7 ($C_{ar}H$), 81.6 (C_{al}), 80.4 (*C*HOCH$_3$), 63.9 (CH), 57.0 (CH_3O), 44.3 (CH_2), 42.4 (CH_2), 41.3 (CH_2); IR (KBr): $\tilde{\nu} =$ 3436 (s; O–H), 1734 (vs; C=O), 1678 (vs; C=O), 1384 (vs), 697 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 366 (35) $[M]^+$, 217 (18) $[M - C_9H_9O_2]^+$, 121 (100) $[C_8H_9O]^+$, 105 (36) $[PhCO]^+$, 77 (44) $[C_6H_5]^+$; elemental analysis calcd (%) for $C_{21}H_{22}N_2O_4$ (366.41): C 68.84, H 6.05; found C 68.94, H 6.12.

***endo*-(5*R*,6*R*)-6-Hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (15b′)**: Yield 141 mg (43%); $R_f = 0.26$ (Et_2O); m.p. 209 °C; ^1H NMR (250 MHz): $\delta = 7.41-7.15$ (m, 10H; arom. H), 5.84 (s, 1H; C*H*OCH$_3$), 4.02–3.86 (m, 2H), 3.57–3.40 (m, 2H), 3.29 (dd, $^3J = 12.4$ Hz, $^3J = 4.5$ Hz, 1H), 3.09 (s, 3H; OCH_3), 2.61–2.46 (m, 1H), 2.35–2.16 (m, 2H); ^{13}C NMR (62.9 MHz): $\delta = 170.3$ (CO), 156.1 (NCON), 140.7 (C_{ar}), 136.3 (C_{ar}), 128.9 ($C_{ar}H$), 128.7 ($C_{ar}H$), 128.6 ($C_{ar}H$), 128.5 ($C_{ar}H$), 128.3 ($C_{ar}H$), 125.5 ($C_{ar}H$), 81.6 (C_{al}), 80.4 (*C*HOCH$_3$), 63.8 (CH), 57.1 (CH_3O), 44.4 (CH_2), 42.9 (CH_2), 40.6 (CH_2); IR (KBr): $\tilde{\nu} = 3435$ (s; O–H), 1734 (vs; C=O), 1684 (vs; C=O), 1384 (vs), 750 (m), 704 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 366 (19) $[M]^+$, 217 (13) $[M - C_9H_9O_2]^+$, 121 (100) $[C_8H_9O]^+$, 105 (21) $[PhCO]^+$, 77 (14) $[C_6H_5]^+$; elemental analysis calcd (%) for $C_{21}H_{22}N_2O_4$ (366.41): C 68.84, H 6.05; found C 68.84, H 5.99.

***endo*-(5*S*,6*S*)-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (12b)**: *endo*-(5*S*,6*S*)-6-Hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (**15b**, 38.0 mg, 0.10 mmol) was dissolved in methanol (5 mL) and treated with K_2CO_3 (21.0 mg, 0.15 mmol). After the mixture had been stirred for 1.5 h at room temperature, silica gel (300 mg) was added and the solvent was removed in vacuo. After chromatographic purification (EtOAc/MeOH 98:2), compound **12b** (17.0 mg, 78%) was obtained as a white solid. $[\alpha]_D^{20} = -92.0$ ($c = 0.6$ in MeOH); $t_R = 25.17$ min (ChiralCel OD, 220 nm).

***endo*-(5*R*,6*R*)-6-Hydroxy-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (*ent*-12b)**: According to the procedure described for the transformation **15b** → **12b**, *endo*-(5*R*,6*R*)-6-hydroxy-3-((*R*)-methoxyphenylacetyl)-6-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one (**15b′**, 70.0 mg, 0.19 mmol) was dissolved in methanol (12 mL) and treated with K_2CO_3 (40.0 mg, 0.29 mmol). After chromatographic purification (EtOAc/MeOH 98:2), *ent*-**12b** (35.0 mg, 84%) was obtained as a white solid. $[\alpha]_D^{20} = +90.1$ ($c = 1.1$ in MeOH); $t_R = 20.33$ min (ChiralCel OD, 220 nm).

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[26] Crystal data of compound **5** ($C_{13}H_{14}N_2O_3$, $M_r = 246.26$): crystal size $0.49 \times 0.21 \times 0.17$ mm, orthorhombic, space group $P2_12_12_1$, $a = 828.4(1)$, $b = 1093.2(1)$, $c = 1319.0(1)$ pm, $U = 1194.5(2)$ Å^3, $\rho_{calcd} = 1.369$ g cm^{-3} for $Z = 4$, $F(000) = 520$, $\mu = 8.2$ cm^{-1}, CAD4 (Enraf – Nonius) diffractometer, $\lambda = 1.54178$ Å, ω scan, 2585 reflections ($\pm h$, $\pm k$, $\pm l$), $2\Theta_{max} = 140.0°$, 2183 independent and 2011 observed reflections [$F \geq 4\sigma(F)$], 220 refined parameters, $R1 = 0.0529$, $wR2 = 0.1455$, residual electron density 0.22 e Å^{-3}, direct methods, hydrogen atoms refined. CCDC 176 337 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

[27] Crystal data of compound *rac*-**10b** ($C_{11}H_{12}N_2O_2$, $M_r = 204.23$): crystal size $0.61 \times 0.57 \times 0.30$ mm, orthorhombic, space group $P2_12_12_1$, $a = 886.5(2)$, $b = 1069.3(2)$, $c = 1070.5(1)$ pm, $U = 1014.8(3)$ Å^3, $\rho_{calcd} = 1.337$ g cm^{-3} for $Z = 4$, $F(000) = 432$, $\mu = 7.7$ cm^{-1}, CAD4 (Enraf – Nonius) diffractometer, $\lambda = 1.54178$ Å, ω scan, 2164 reflections ($\pm h$, $\pm k$, $\pm l$), $2\Theta_{max} = 140.2°$, 1810 independent and 1774 observed reflections [$F \geq 4\sigma(F)$], 185 refined parameters, $R1 = 0.0495$, $wR2 = 0.1322$, residual electron density 0.28 e Å^{-3}, direct methods, free refinement for hydrogen atoms. CCDC 176 338 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

[28] Crystal data of compound *rac*-**12a** ($C_{12}H_{14}N_2O_2$, $M_r = 218.25$): crystal size $0.52 \times 0.34 \times 0.22$ mm, monoclinic, space group $P2_1/n$, $a = 1024.9(1)$, $b = 959.7(1)$, $c = 1194.6(1)$ pm, $\beta = 114.31(1)°$, $U = 1070.8(2)$ Å^3, $\rho_{calcd} = 1.354$ g cm^{-3} for $Z = 4$, $F(000) = 460$, $\mu = 7.6$ cm^{-1}, CAD4 (Enraf – Nonius) diffractometer, $\lambda = 1.54178$ Å, ω scan, 2004 reflections ($\pm h$, $+k$, $-l$), $2\Theta_{max} = 140.0°$, 1786 independent and 1648 observed reflections [$F \geq 4\sigma(F)$], 154 refined parameters, $R1 = 0.0596$, $wR2 = 0.1701$, residual electron density 0.38 e Å^{-3}, direct methods, calculated positions for C–H, free refinement of O2–H1 and N2–H2. CCDC 176 339 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

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[31] Crystal data of compound **15a** ($C_{21}H_{22}N_2O_4$, $M_r = 366.41$): crystal size $0.45 \times 0.20 \times 0.20$ mm, orthorhombic, space group $P2_12_12_1$, $a = 1105.1(1)$, $b = 1143.3(1)$, $c = 1474.9(1)$ pm, $U = 1863.0(3)$ Å^3, $\rho_{calcd} = 1.306$ g cm^{-3} for $Z = 4$, $F(000) = 776$, $\mu = 7.4$ cm^{-1}, CAD4 (Enraf – Nonius) diffractometer, $\lambda = 1.54178$ Å, ω scan, 2672 reflections ($\pm h$, $\pm k$, $\pm l$), $2\Theta_{max} = 140.0°$, 2535 independent and 2393 observed reflections [$F \geq 4\sigma(F)$], 251 refined parameters, $R1 = 0.0412$, $wR2 = 0.1099$, residual electron density 0.22 e Å^{-3}, direct methods, calculated positions for hydrogen atoms refinement of H1. CCDC 176 340 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.uk).

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[33] In addition, it is conceivable that the hydrogen abstraction already occurs enantioselectively in a substrate **8** bound to the host **3**. The C–C bond would subsequently form at the same enantiotopic face at which the hydrogen atom abstraction has occurred. The stereochemical outcome would be qualitatively identical. Currently, we cannot tell whether this pathway is selectivity-determining or whether, as suggested in the narrative, it is the combination of the biradical centers, or whether both pathways operate simultaneously. Studies to clarify this mechanistic detail are underway.

[34] Note that by CIP nomenclature the (6*R*) configuration in *ent*-**9a** corresponds to the (6*S*) configuration in *ent*-**11a** and in *ent*-**12a**.

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